Menopause and Hormones

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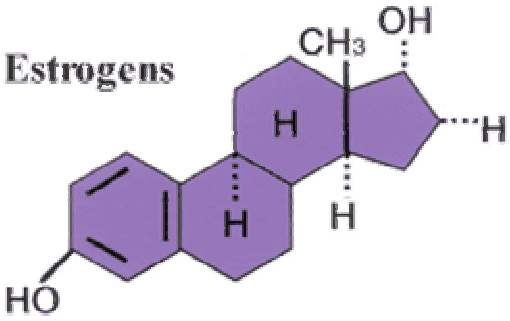
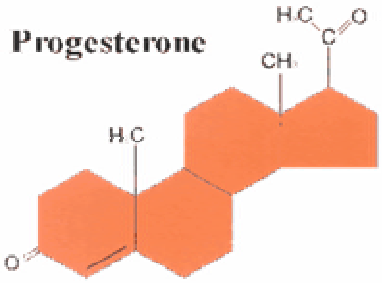
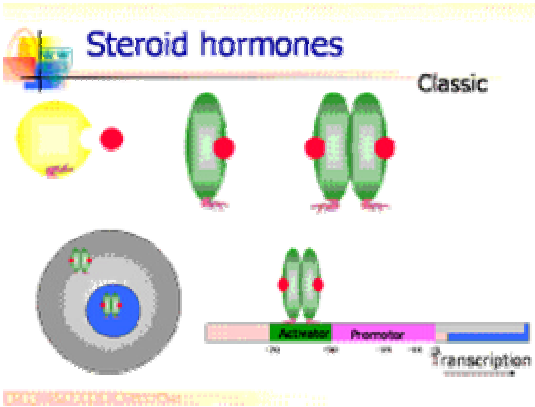
Sex steroid hormones





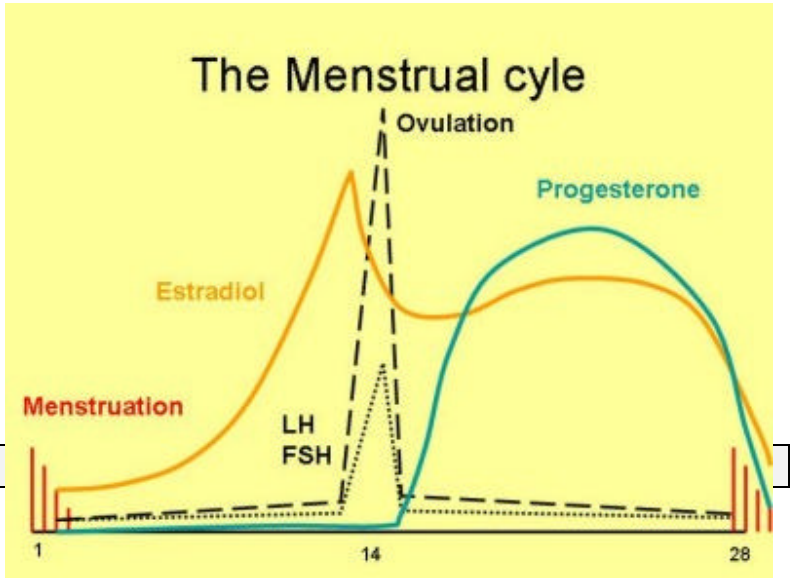
Steroid hormones have a typical chemicalstructure. Their mechanism of action is through binding to a specific receptor which in the nucleus of the cell will induce effects at the genomic level.
Slight differences in structure fundamentally change the effects, which can be corticoid, androgen, progestagen or estrogen. The latter 3 are called sex steroid hormones. Each type of sex steroid hormoneis composed of a group of molecules, with slightly different effects.
Sex steroid hormones are secreted by the ovary and by the adrenal gland.
Oestrogens are the typical female hormone which will stimulate breast development, and growth of the uterus and the endometrium causing menstrual bleedings.
Progestagens modulate the effect of the estrogens, eg in the endometrium.



Androgens are the typical male hormones.

The menstrual cycle

The menstrual cycle can best be compared to a domino system : once the oocyte start to develop a cascade of events will lead to



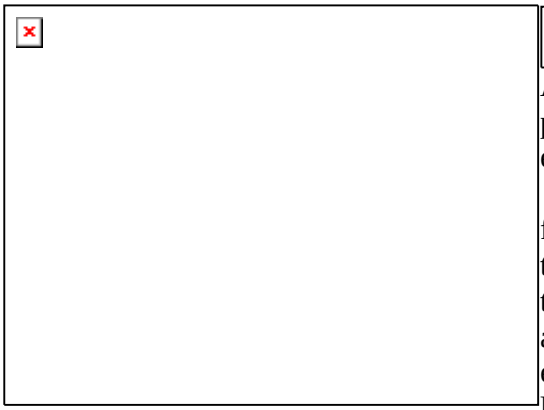
1. oestrogen secretion inherently linked to follicular development
2. ovulation.
3. After ovulation the follicle is transformed into a corpus luteum, which is associated with secretion of progesterone.
4. In the absence of a pregnancy the corpus luteum will die after 14 days, oestrogen and progestagen go down, and a menstruation occurs

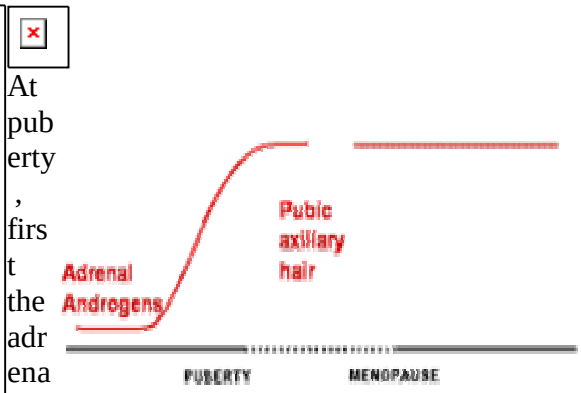
Oestrogens make the endometrium grow ; progestogens stop the growth and modulate the estrogen effect. When the concentrations suddenly decrease a menstruation occurs the so-called steroid deprivation bleeding.

The oocytes

The secretion of estrogens and progestagens thus is strictly linked to the growth of follicles and thus the presence of oocytes. A woman is born with a limited amount of oocytes, which are progressively used. Around 50 years o oocytes are left in the ovary and menopause occurs.

Puberty and Menopause





At puberty, first the adrenals start to secrete androgens, which cause the growth of pubic and axillary hair. Subsequently the ovaries start to secrete estrogens. Low concentrations are sufficient to induce breast growth; higher concentrations are necessary to have regular cycles. Menopause starts when no oocytes are left in the ovary. Menopause thus is a mirror image of puberty, with this difference that androgen secretion from the adrenals continues after menopause. This androgen secretion is partially converted into low concentrations of oestrogens eg in fat tissue. These low concentration of estrogens are sufficient to prevent breast involution.
Another source of androgen secretion in women are the ovaries : for this reason some gynaecologists prefer not to remove the ovaries during hysterectomy unless indicated because of the risk of ovarian cancer.

Hormone Replacement Therapy

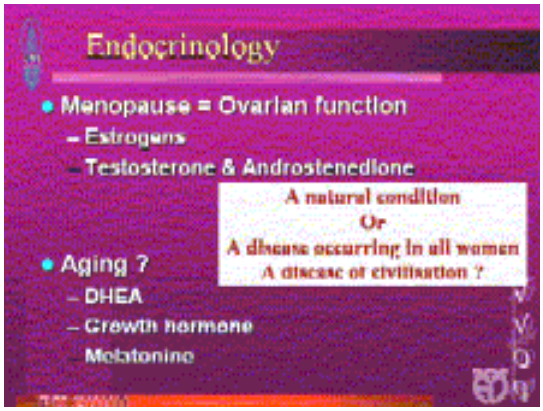
HRT versus HT

It is important to realize that hormone replacement therapy (HRT) is used in 2 significances

1. **to replace the hormones which are no longer secreted**. This means that doses, type, and sequences are given as during the menstrual cyle. We can compare this to wearing glasses, which compensate for the lens.
2. The second meaning of HRT is to take hormones **to treat or to prevent symptoms**. In this approach hormones are given as a drug, ie not too much and not longer than necessary.
3. A third meaning is HTR to prevent aging : also this is preventive medecine

Underlying to these opposing approaches is a fundamental question **:** should hormones at menopause be replaced ? **are** we not doing something against nature ?

1. let us assume we could modify the rate of oocyte consumption. We then could decide whether menopause would occur at age 40, 50, 60 or later.
2. In nature everything is programmed with some excess : considering that we are mammals is is striking that in mammals menopause does not occur, unless when we introduce artificial housing, feeding etc ie in captivity. This strongly suggest that we were not programmed to become older than fifty : a woman survives her ovaries. Replacement is clearly needed.

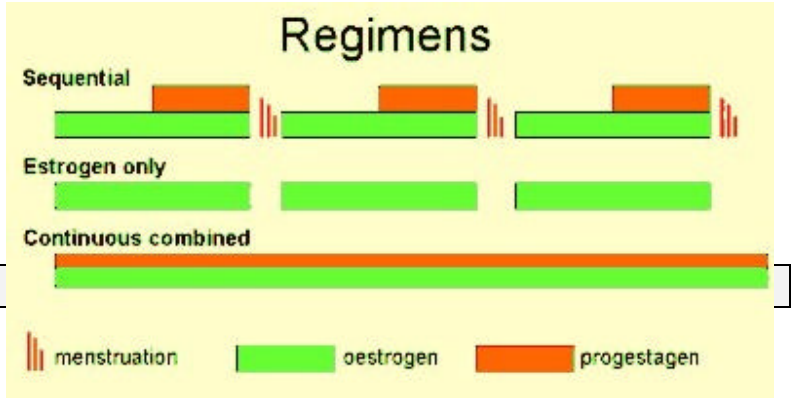


I am a strong believer that the approach to menopause should be replacement. This does not exclude that variations in treatment can be given in order to respond to specific demands, eg decrease blood loss, premenstrual syndrome.

I even believe that for many women hormones can better be given thean their own natural production : many things are given us by nature, like the color of eyes, which does not mean that another color could not be preferred.

Treatment regimens

Sequential **oestrogen-progestagen** treatment This clearly mimics the menstrual cycle : a period

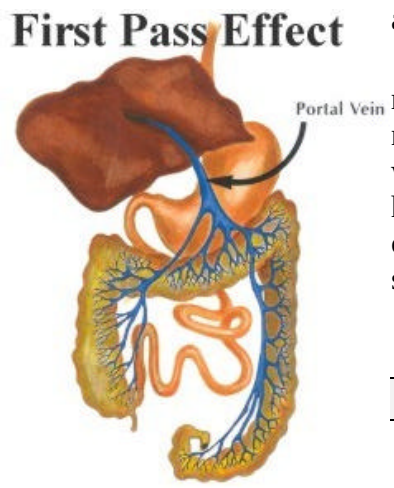


of 12 days of oestrogen is followed by 12 days of estrogen+progesterone, and 4 days without treatment. Mimicking the menstrual cycle means all the symptoms of a menstrual cycle such as a menstruation, for some women premenstrual tension, mood changes etc..
Oestrogen only treatment
If a woman has undesired side effects of progestagens such as breast tenderness, bloating, mood changes etc (like in a normal menstrual cycle) progestagens can be omitted. This implies that the protective effect of progestagens upon the endometrium is no longer present : in general it is widely accepted that the unopposed estrogen effect increases slightly the risk of endometrial cancer. To judge and prevent this risk an individualized regimen should be discussed, with following elements
- in the absence of a uterus the risk clearly does not exist
- the dose of estrogen given should not be too high
- the endometrial growth can be followed by ultrasound or endometrial biopsy.

Continuous combined Therapy
In order to prevent menstrual bleeding, oestrogens and progestogens can be given simultaneously and continuously. These therapies are all associated with irregular bleeding/spotting initially in 30% and after 6 months still in 10% of women.
Other therapies
SERMS specific estrogen eceptormodulators. Estrogens have 2 types of receptors one for brain, breast and uterus, and another for bones and cardiovascular. SERMS try to be specific for the second type of receptor.
LIVIAL

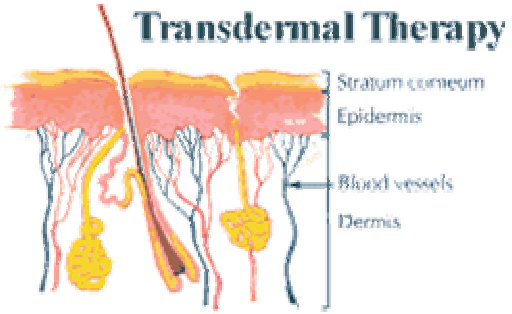
Which hormones are used ?

Oestrogens : the natural hormones are 17b-estradiol, estrone and estriol (less active). Oestradiol is so poorly soluble in water that it has to be micronised to be resorbed after oral intake. Solubility can be increased by chemical transformation eg ethinyl-estradiol (very active – the hormone used in oral contraception), eg estradiol-valerate, eg conjugated estrogens (mainly estrone)
Progestagens. Progesterone is so insoluble in water that it poorly resorbed after oral intake unless micronised. Therefore most of the progestagens used are slightly chemically altered. The products used are derivatives of progesterone and derivatives of nor testosterone (most frequently used in oral contrqceptives).
Androgens. Androgens are rarely used in HRT. DHEA belongs to the group of weak androgens, but its indication is yet unclear.



Which route of administration ?

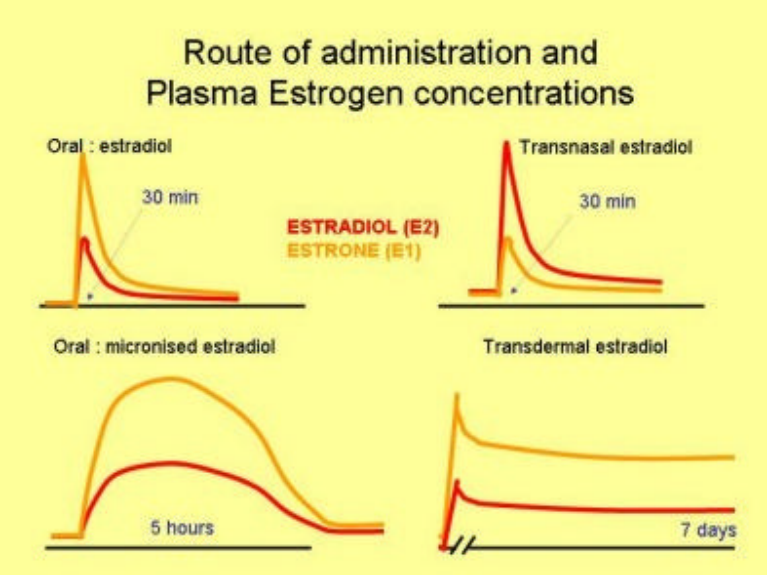
-**oral** : this route necessarily will result in higher liver concentrations since steroids



which are resorbed have to pass through the liver. Moreover some hormones are metabolised during this passage, eg estradiol is almost quantitatively transformed into estrone during one liver passage. Therefore after oral intake of estradiol, the plasma hormone will be predominantly estrone. This does not occur when the 17 position of estadiol is blocked eg in ethinyl-estradiol. This phenomenon is known as the first pass effect in the liver

- **Transdermal**: the skin acts as a reservoir from which steroids are slowly but continuously released, thus avoiding the first pass effect in the liver. The plasma concentrations thus are almost constant over the day.

- transvaginal : this administration is similar to transdermal administration, but the uterine concentrations are slightly higher, known as "the first pass effect in the uterus"



- transnasal : this is a newer method of administration. It is comparable to oral administration since resorbtion is fast with a peak after some 30 min. It is comparable to transdermal therapy since it avoids the first pass effect in the liver

Conclusion and **interpretation :** It is unclear whether

-the first pass effect in the liver should be avoided in all women. In women with specific risks, it might be wiser to avoid a first pass effect in the liver.

-a continuous or a pulsed plasma concentration should be preferred. Today we know that the effects are not identical but little evidence exist for specific clinical preferences.

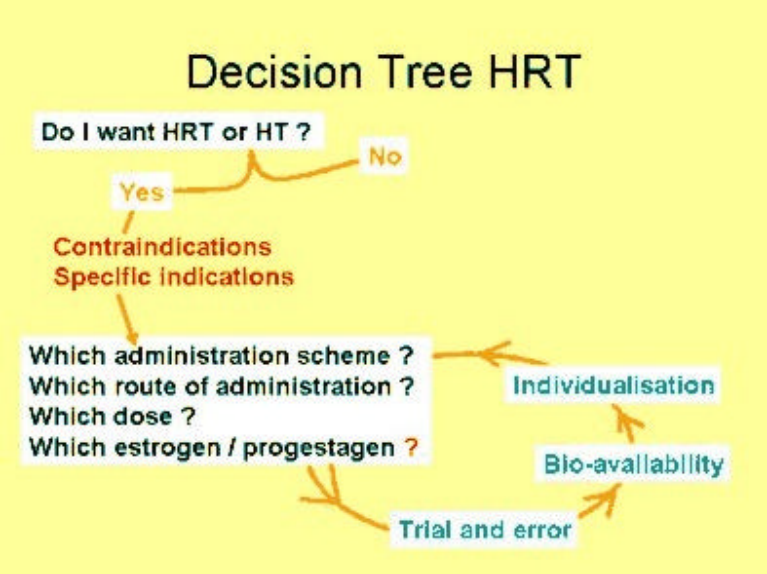
Which doses should be used?

Individualisation of therapyaims to find the ideal dose, route of administration, hormone combination, and treatment regimen for the individual woman.Denying this is like giving the same dress, in the same colour to all women.

This is not so easy, because of the variable bio-availability. This phenomenon is well known, but difficult to translate into clinical practice : for both estrogens and progestagens the concentrations in blood achieved with the same dose, vary at least 2 times for 65% of women, 4 times for 25% and more for 10%. This means that 1 mg/day can mean for some women exactly the same dose as 4 mg for other.

Practical decision tree for the use of Hormones

1. Should I take hormones ?



This is a individual decision based upon personal preferences, upon the assessment of risks and benefits of a specific woman, and upon eventual contraindications.

Indications :

The indication to take hormones can **be the quality of life**, 'I feel better' sexuality, vasomotor symptoms and sleep disturbances. Since most other parameters as memory, brain function etc are highly subjective and difficult to measure, it is logical that the effectiveness of HRT for these is poorly documented and certainly not clearly demonstrated. It is important to stress, however, that 'not demonstrated' does not mean 'not true'. A discussion about this can be found under 'evidence based medecine'. This aspect can probably best be illustrated by the statement 'with HRT I not only feel younger, **I also look younger'**. That women taking HRT effectively look younger has never been demonstrated clearly, although the increase in skin thickness and collagen, suggest the statement will probably be correct.

The indication can be **osteoporosis,** both prevention of loss or prevention of further loss in women already osteoporotic. The effectiveness of estrogens, and the superiority in comparison with calcium, vitamin D and exercise (although all three important) is clearly demonstrated.

Contra-**indications :**

A contra-indications to take hormones is a condition which is an indication to remove the ovary (or a radiocastration) in women with an ovarian cycle. Traditionally a history of breast cancer constituted a contra-indication, but this has become questioned over the last years.

All other 'so called' contra-indications are relative : eg a fibroma of the uterus. There is no doubt that a fibroma can increase in volume by estrogens and that without estrogens a fibroma will decrease in volume. Since in younger women a fibroma is an indication of hysterectomy while leaving the ovaries and the ovarian function intact, it can be argued that also in older women this is rather an indication for hysterectomy than a contra-indication for HRT. In this group of relative contra-indications, it is wise to discuss with your doctor, your individual risk for cardiovascular accidents, for deep venous thrombosis etc.

2. Which hormones, how much, which regimen.

The first decision is whether to take HRT or HT.

With HT, minimal amounts of estrogen only are taken. “not more than necessary ; as little as possible” These generally are sufficient to decrease vasomotor symptoms and vaginal dryness.

After the decision to take HRT, comes the question ‘which treatment ?’ With HRT it should be discussed and generally evaluated by trial and error, whether it is preferable to take hormones orally or transdermally or transnasally. The second choice is the type of estrogens (micronised estradiol, estradiol, estradiol-valerate, conjuged estrone, estriol) and progestagen (> 15 different products available, each with a specific profile varying from pure progestagenic to in addition slichtly androgenic, anti-androgenic, anti-mineralocorticoid) and the dose and regimen of application of these products. It clearly is too complex to list all possible combinations : moreover not all are available in each route of administration, in all combinations or regimens. Most of the products are indeed combination products, developed by the industry in fixed doses, regimens and products.

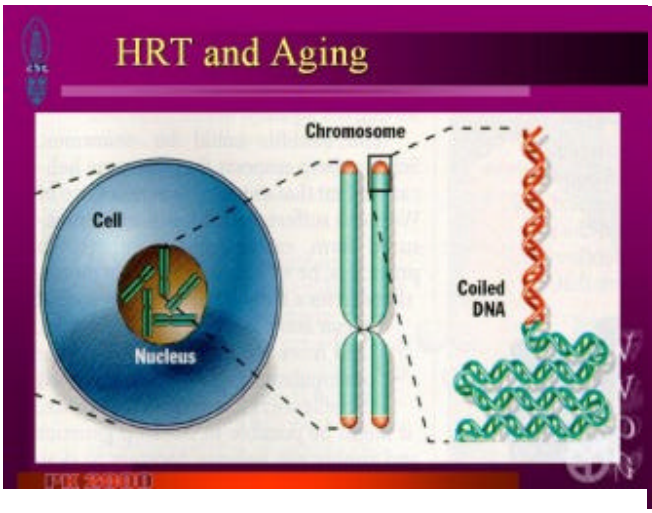
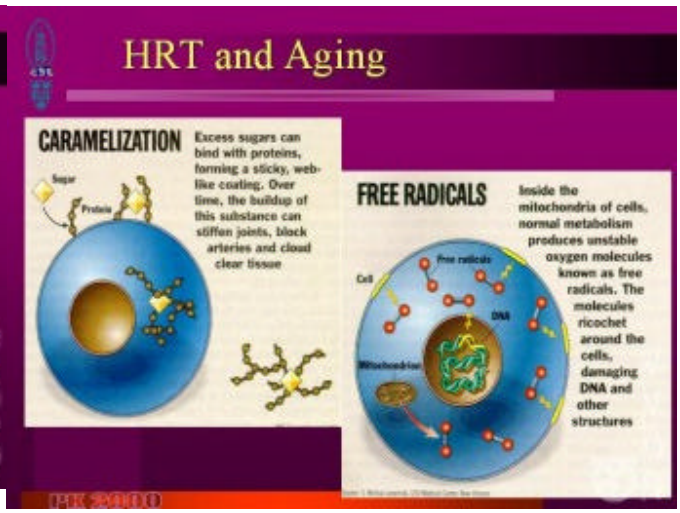
What is the best treatment for **me ?**

“Each of us is born with a specific color of hair, eyes etc. These are genetically given and cannot be changed. Even if you would like to have a different ***colour*** of eyes, you will have to live with the inherited ***colour***. I believe the same hold true for the hormonal balances which are individual for each of us. It also implies that our genetically given constitution is the best for us. It also ***suggest*** that HRT and the different doses, products and application offer the possibility to find an even better equilibrium than ever before.’

To find this optimal an individualized treatment for you should be the aim of your doctor.

To give a flavour of the possibilities :

1. intake of transnasal or oral non micronised products, the plasma concentrations rise sharply with a peak after 30 min. After intake if micronised products, the resorbtion is much slower with broad maximal concentrations after several hours. It is known that the same dose as peak concentrations and as continuous concentrations can have different effects. The individual appreciation, however, cannot be predicted.
2. After oral intake of any estrogen (except ethinyl-estradiol, and estriol) the first pass effect in the liver transforms most of the estradiol into estrone.
3. Since industry want to avoid side effects and because of the variable and unpredictable bio-availability, all commercially available products are globally underdosed in estrogens and overdosed in progestagens. The dose chosen indeed is not the ideal dose for 50% of the women, but the dose with the least side effects for over 90% of women.
4. Fine tuning can be achieved by knowledge of products, by combination of products and by individualizing. The following is an examples of this. To achieve a physiological estradiol/estrone ratio in blood, a combination of ethinyl-estradiol and estradiol can be given. By increasing/decreasing the doses and trying different progestagens. HRT, is like bying a new dress : difficult to make a final choice before trying. Since HRT is far more complex than contraception, guidance by a professional is necessary.

Aging versus HRT

HRT will not prevent aging : then mechanisms of aging are totally different such as free radicals, caramelisation, or shortening of telomeres. It is actually unclear what the role of melatonin and DHEA is.